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REVIEW/MISE AU POINT

Effects of repetitive peripheral magnetic stimulation on normal or impaired motor control. A review

Influence des stimulations magnétiques périphériques répétitives sur le contrôle moteur normal ou déficient. Revue de littérature

L.D. Beaulieu, C. Schneider*

Clinical neuroscience and neurostimulation laboratory, centre de recherche du CHU de Québec, Université Laval, Faculty of Medicine, Departement of Rehabilitation, 2705, boulevard Laurier, RC-9800, G1V 4G2 Quebec, Canada

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KEYWORDS
Repetitive peripheral magnetic stimulation;
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Summary
Introduction. — Repetitive magnetic stimulation at the periphery (rPMS), i.e. over spinal roots, nerves or muscles, represents a new painless and noninvasive approach that can contribute to motor recovery. This method is based on the assumption that, under rPMS, neural networks involved in motor control would be regulated by the large recruitment of proprioceptive afferents, with little activation of cutaneous receptors.
Study aim. — This literature review dealing with rPMS after-effects on motor control aimed at better understanding the outcome measures and further discussing some possible involved mechanisms.
Results. — Our literature search resulted in 13 studies that used different types of outcomes (neurophysiological, biomechanical, clinical) to test the influence of rPMS over spinal roots or muscles in healthy individuals and in persons with stroke or spinal disorders. Dynamic changes were reported post-rPMS, such as spasticity reduction and improvements of movement dynamics. Studies also brought about some interesting insights on the cortical plasticity associated with rPMS effects, such as the activation of fronto-parietal loops that may explain the post-rPMS improvement of motor planning.
Conclusions. — Due to the heterogeneous and scant literature on the topic, no conclusion can be drawn to date. However, the results encourage the concurrent testing of clinical, neurophysiological and biomechanical outcomes to investigate more precisely the relevance of rPMS in neurological rehabilitation.

* Corresponding author.
E-mail address: cyril.schneider@rea.ulaval.ca (C. Schneider).

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MOTS CLÉS
Stimulation magnétique périphérique répétitive ;
Désordres moteurs ;
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Afférences sensorielles

Résumé
Introduction. — La stimulation magnétique répétitive périphérique (rPMS) (c'est-à-dire appliquée sur des racines nerveuses, des nerfs ou des muscles), représente une méthode indolore et non invasive pouvant contribuer à la récupération motrice. Le principe à la base de cette méthode est que la rPMS permettrait le recrutement d'afférences proprioceptives, avec peu d'activation des récepteurs cutanés, ce recrutement étant à la base d'une régulation des réseaux neuronaux du contrôle moteur.
But de l'article. — Améliorer la compréhension de la manière de mesurer les changements induits par la rPMS et discuter des mécanismes sous-jacents à ceux-ci.
Résultats. — Nous reprenons les résultats de 13 études qui ont utilisé différents types de mesures (neurophysiologiques, biomécaniques, cliniques) pour tester l'influence de la rPMS appliquée sur des racines nerveuses ou des muscles chez des personnes neurologiquement normales ou ayant présenté un accident vasculaire cérébral ou des pathologies médullaires. Ces études font état de changements dynamiques survenant après rPMS, comme une diminution de la spasticité ou l'amélioration de certaines composantes dynamiques du mouvement. Les études ont aussi proposé certaines pistes de réflexion intéressantes sur la plasticité corticale associée aux effets rPMS, telle que l'activation de circuits fronto-pariétaux qui pourrait expliquer les améliorations de planification motrice.
Conclusions. — Vu l'hétérogénéité et la quantité limitée d'études sur le sujet, aucune conclusion ne peut être tirée à l'heure actuelle. Les résultats constituent cependant un encouragement à l'utilisation conjointe d'outils cliniques, neurophysiologiques et biomécaniques pour investiguer plus précisément la pertinence de la rPMS en réadaptation neurologique.

Introduction

Repetitive magnetic stimulation at the periphery (rPMS), i.e. over spinal roots, nerves or muscles is gaining popularity in clinical neurological research as a new painless and noninvasive approach to activate proprioceptive afferents with little activation of cutaneous receptors [24,45]. rPMS has been used for almost two decades in humans in order to understand the changes of motor function under peripheral stimulation and question the underlying mechanisms of action that may contribute to motor control improvement in physiopathology. It is mainly proposed that peripheral recruitment of sensory afferents generates cortical somesthetic reactivation that may improve sensorimotor integration in persons with stroke [42,44], or down-regulate the hyperactive spinal excitability in persons with spinal cord disorders [19,33]. However, the functional impact of rPMS remains difficult to overview because good quality evidence remains scarce, each rPMS study having focused on a different neurological population and testing different outcomes under different parameters of stimulation. Thus, there is a gap between the insufficient understanding of rPMS influence on motor control (e.g., which components of movement are improved) and the dire need in clinical research of protocols testing rPMS in larger samples. Therefore, the aim of the present work was to review all studies dealing with rPMS influence on motor control and document the different outcome measures tested in healthy humans and persons with motor impairment caused by central nervous system (CNS) lesion or disease. RPMS influence on normal and impaired motor control is discussed in both terms of clinical relevance and potential mechanisms of action.

Methods

Our literature search on rPMS papers used the terms (repetitive peripheral magnetic stimulation) OR (repetitive spinal magnetic stimulation) with no imposed time restriction and the EBSCOhost website hosted the selection of MEDLINE, CINAHL and SPORTDiscus databases and automatically removed duplicates. Additional relevant studies were also hand-searched in the references list of the papers selected for the review. The inclusion criteria were full-text original papers written in English and about repetitive magnetic stimulation applied to nerves, muscles or spinal roots, both in healthy individuals and in persons with motor impairments caused by CNS lesion or disease. The exclusion criteria were any study with other devices than focal magnetic stimulators (e.g., pulsed magnetic fields), with single peripheral magnetic stimulation (i.e. not a repetitive pattern), repetitive magnetic stimulation to scalp, and studies that did not focus on motor control. Inclusion and exclusion criteria were applied using title and abstract, and if necessary, full text.

The literature search was ended in September 2012 and had resulted in 244 papers. Two hundred and thirty-three papers were excluded for methods other than rPMS ($n = 202$), not full-text original papers written in English ($n = 17$) and not papers focusing on motor control ($n = 14$). One paper that applied rPMS to persons with chronic pain syndrome [20] was not excluded for the relevant data obtained in a group of healthy participants. The remaining 11 papers were included in the review and two supplementary papers were found in the references list. Thirteen rPMS papers were thus reviewed for the present work.

Table 1 Studies that applied rPMS over spinal roots.

Authors	Location of rPMS	Participants	Sample size	Outcome measures
Experimental design				
Nielsen et al., 1996 [34]	Midline, caudal part of the coil at T8	MS	38	AS, EMG, MVC, ADL
Quasi-experimental design				
Nielsen et al., 1995 [32]	Midline, caudal part of the coil at T8	MS	12	AS, EMG, MVC, ADL
Nielsen and Sinkjaer, 1997 [33]	Midline, caudal part of the coil at T8, and L3	MS HS	11 9	H-reflex, TMS
Krause et al., 2004 [19]	2 cm paravertebral between L3 and L4	VSD HS	15 16	MAS, PTS
Krause et al., 2005 [20]	Paravertebral, over cervical nerve roots[a]	HS	10	TMS
Krause and Straube, 2008 [22]	Paravertebral, over C7 and C8	HS	15	TMS
Case study design				
Krause and Straube, 2005 [21]	Paravertebral, over lumbar nerve roots[a]	SCI	1	MAS, PTS

rPMS: repetitive peripheral magnetic stimulation; T8: eighth thoracic vertebrae; MS: multiple sclerosis; AS/MAS: ashworth scale/modified ashworth scale; EMG: electromyography; MVC: maximal voluntary contraction; ADL: activities of daily living; L3/L4: third and fourth lumbar vertebraes; HS: healthy subject; TMS: transcranial magnetic stimulation; VSP: various spinal diseases; PTS: Wartenberg pendulum test of spasticity; C7/C8: seventh and eighth cervical roots; SCI: spinal cord injury.
[a] No other detail.

Results: selected studies

RPMS was applied over spinal roots in seven studies (Table 1) or over a muscle belly in six studies (Table 2). Table 3 presents the selected rPMS parameters in each study. The rPMS after-effects are presented below for spinal roots stimulation and for muscle belly stimulation in healthy individuals (normal motor control) and in persons with stroke or spinal disorders (impaired motor control). The design of each study informed on the internal validity and strength of the evidence [38]: two studies were considered experimental (or randomized) with participants randomly assigned to at least two comparison groups; eight studies without random assignment or comparison group were considered quasi-experimental and three were case studies (single-subject design).

RPMS in normal motor control

Over spinal roots

Four studies used quasi-experimental designed protocols to test the effects of rPMS applied over spinal roots. Krause et al. [19] used the modified Ashworth scale (MAS) and the Wartenberg pendulum test (Table 4) to assess the changes of muscle resistance to stretch after rPMS over the lumbar spine ($n = 16$ healthy volunteers). The authors did not observe any change in MAS during the two-hours measurements post-rPMS but they detected a slight increase of the first swing velocity (pendulum test) in both legs. Nielsen and Sinkjaer [33] tested the changes of spinal reflex excitability ($n = 9$ participants) and the changes of corticospinal excitability ($n = 3$ participants) before and after rPMS applied over thoracic nerve roots. Spinal excitability was assessed by means of the soleus Hoffmann reflex (H-reflex, Table 4) and the authors detected a significant reduction of H-reflex amplitudes that appeared to be maximal at 500 ms after rPMS and lasted up to 5 s [33]. Corticospinal excitability was tested by means of transcranial magnetic stimulation (TMS, Table 4) and the authors showed that the amplitudes of the soleus motor evoked potentials (MEP) were significantly increased at 10—500 ms after rPMS in one subject but unchanged in the two others. Krause et al. [20] used TMS to investigate the effects of rPMS on the cortical silent period (cSP), which informs on cortical motor inhibition (Table 4). RPMS applied over the cervical roots significantly lengthened the cSP in the forearm extensors. Krause and Straube [22] applied rPMS over the right cervical roots and used TMS to test the influence on corticospinal excitability on both sides for an intrinsic hand muscle. They showed that the after-effects were specific to the side stimulated with changes of M1 excitability only for the right hand (TMS of contralateral left hemisphere): MEP amplitudes were increased (up-regulation of corticospinal excitability) and cSP were lengthened (increase of $GABA_B$ inhibitory activity in M1, replication of previous results [20]); the use of the double TMS paradigm also helped detect that the short-interval intracortical inhibition was increased ($GABA_A$ inhibition of pure cortical origin [23]).

Table 2 Studies that applied rPMS directly over muscles.

Authors	Location of rPMS	Participants	Sample size	Outcome measures
Experimental design				
Behrens et al., 2011 [5]	Soleus	HS	24	H-reflex
Quasi-experimental design				
Struppler et al., 2003 [42]	Extensor indices proprius	SK	52	MAS, EMG, ROM, angular velocity
Struppler et al., 2004 [41]	Triceps/biceps brachii	HS	13	EMG, RAS
Struppler et al., 2007 [43]	Finger/hand extensors	SK	8	EMG, ROM, angular velocity, PET scan with rCBF
Case study design				
Havel and Struppler, 2001 [15]	Extensor indices proprius	SK	1	EMG, ROM, angular velocity
Bernhardt et al., 2006 [6]	Flexors/extensors of forearm/upper arm	SK	1	ROM, angular velocity, movement torque

rPMS: repetitive peripheral magnetic stimulation; HS: healthy subject; SK: stroke; MAS: modified ashworth scale; EMG: electromyography; ROM: range of motion; RAS: resistance against stretching; PET scan: positron emission tomography; rCBF: regional cerebral blood flow.

Table 3 RPMS parameters.

Authors	Coil type	ON/OFF (s)	Duration (min)	Frequency (Hz)	Intensity (T)	Number of sessions
Experimental design						
Nielsen et al., 1996 [34]	RC	8/22	25	25	1.05—1.26	14[a]
Behrens et al., 2011 [5]	RC	6.6/2	2.52	15	NM	1
Quasi-experimental design						
Nielsen et al., 1995 [32]	RC	8/22	30	12	0.95—1.2	1
Nielsen and Sinkjaer, 1997 [33]	RC	NA, Single MS	NM	NA	1.26	1
	RC	NA, 16 MS	NM	25	1.26	1
	RC	5/5	5	25	1.26	1
Struppler et al., 2003 [42]	Fof8	1.5/4	15	20	NM	1
Struppler et al., 2004 [41]	Fof8	1.5/3	12.5	20	1.2	1
Krause et al., 2004 [19]	RC	10/40	~8.5	20	NM	1
Krause et al., 2005 [20]	RC	10/60	10	20	NM	1
Struppler et al., 2007 [43]	Fof8	1.5/4	~15.5	20	1.2	2
Krause and Straube, 2008 [22]	RC	10/NM[b]	NM	20	NM	1
Case study design						
Havel and Struppler, 2001 [15]	Fof8	1.5/NM[c]	NM	20	NM	NM
Krause and Straube, 2005 [21]	NM	10/60	10	20	NM	12[d]
	NM	10/60	15	15	NM	
	NM	10/60	20	10	NM	
Bernhardt et al., 2006 [6]	RC	1.5/3	15	20	NM	1

rPMS: repetitive peripheral magnetic stimulation; ON/OFF: alternate phases of stimulation/no stimulation; RC: Round coil; NM: not mentioned; NA: not applicable; MS: magnetic stimulation; Fof8: figure of eight.

[a] Two sessions per day for seven consecutive days.

[b] Ten series of 10 s each, OFF time not mentioned.

[c] Approximation of 70 cycles of 1.5 s each.

[d] One session per week over 12 weeks; nine rPMS sessions and three sham sessions in a random order.

Table 4 Brief description of some tools/outcomes testing rPMS after-effects.

Tools	Description
Ashworth Scale (AS), Modified Ashworth Scale (MAS)	AS and MAS consists of the clinician's subjective interpretation of spastic muscle resistance against rapid passive stretching by means of a 4-level (AS) or 5-level (MAS) ordinal scale [7]
Wartenberg pendulum test	The participant is relaxed, sitting or supine, with the knees at the edge of the table; the evaluator lifts the knee-ankle segment until complete extension of the knee, then releases it against gravity, and the free swings are recorded by an electrogoniometer until immobilization [3]
Electromyographic (EMG) recordings	EMG data by means of surface electrodes in a monopolar or bipolar configuration is often used as the gold standard reference for the validation of other tools in spasticity assessment [7]: EMG activity during active tasks or EMG recordings of spastic muscles responses to passive slow stretch (driven by automated platform or by experimenters)
Hoffmann reflex (soleus H-reflex)	Electrical analogue of stretch reflex: the myotatic reflex loop is activated but anodal stimulation of the tibial nerve at the popliteal fossa bypasses muscle spindles and directly activates sensory and motor fibers [16] Two reproducible responses can be elicited in soleus muscle at intensities sufficient to reach depolarization threshold of sensory fibers and alpha-motoneurons respectively At 8-10 ms after anodal stimulation, the direct motor response (M-response) results from direct recruitment of motoneurons axons and its amplitude is proportional to the portion of tibial nerve activated, thus witnessing stimulus efficacy [39] At 30—33 ms, the H-reflex results from recruitment of sensory fibers and its amplitude depends on the number of Ia-fibers recruited, on the synapse between Ia-fibers and alpha-motoneurons and on the alpha-motoneurons excitability itself, thus reflecting the overall excitability of soleus spinal circuitry [16]
Transcranial magnetic stimulation (TMS)	TMS is a transient time-varying magnetic field that passes through the scalp with little attenuation and without pain so that cortical areas can be easily stimulated [18]. Especially, the activation of corticospinal cells of M1 elicits motor evoked potentials (MEP) in contralateral muscles that are recorded by EMG The MEP size informs on the combined excitability of M1 cells and motoneurons connected in spinal cord [4] The cortical silent period (cSP) is the EMG silence (ms) that follows a MEP superimposed on the tonic activity of a preactivated muscle [9]. CSP depends on the activity of M1 inhibitory interneurons working with $GABA_B$ receptors [13,36]

Over muscles

Behrens et al. [5] proposed the only study to date with a randomized double-blinded sham-controlled design to test the rPMS after-effects in normal motor control. Twenty-four healthy individuals were allocated to rPMS group or sham and stimulation was applied over the soleus muscle belly. Spinal excitability was tested by means of the soleus H-reflex directly before and 2 min after rPMS or sham. No effect was reported for H-reflex amplitudes but a decrease of maximal M-responses (direct recruitment of motoneuron axons, Table 4) was significant in the rPMS group ($P = 0.027$) and marginal in sham ($P = 0.061$). The authors did not comment sham results and concluded that rPMS over muscles did not influence spinal excitability but rather altered neuromuscular propagation.

Struppler et al. [41] used a quasi-experimental designed protocol to evaluate whether rPMS of skeletal muscles could influence muscle tone itself. Thirteen participants were non-randomly allocated to three groups for rPMS applied over the biceps brachii (group A, $n = 9$), the triceps brachii (group B, $n = 7$), or no rPMS (group C, $n = 7$). It was shown that the resistance and the EMG responses of the elbow flexors and extensors to very slow passive stretching (forearms strapped on an automated platform) were significantly increased

after rPMS for group A whereas decreased for group B. The lack of effect for group C precluded that repeated measures explained the effects.

RPMS in impaired motor control

Over spinal roots

Nielsen et al. [34] proposed the only study to date with a randomized double-blinded sham-controlled design to test rPMS influence on the impaired motor control. Thirty-eight persons with multiple sclerosis were randomly allocated to rPMS applied over mid-thoracic nerve roots ($n = 21$ participants) or to sham ($n = 17$ participants, a 15-cm plastic tube was inserted between stimulator and skin). The protocol consisted of 14 sessions of rPMS or sham over 7 consecutive days. At day 1 after the end of stimulation, the Ashworth scale (AS, Table 4) showed a maximal decrease of resistance of the hip, knee and ankle flexors and extensors on both sides in the rPMS group, and with a return to baseline at days 8 and 16. The soleus EMG responses to stretching at different velocities (7.5—120°/sec, foot strapped on a motorized pedal) were also evaluated and the threshold velocity inducing a stretch reflex was increased at days 1 and 8 post-rPMS and returned to baseline at day 16. The amplitude of the stretch reflex was not influenced, neither was the maximal voluntary contraction (MVC) of plantar and dorsal flexors of both ankles (foot strapped on a strain gauge-equipped pedal). Sham did not influence.

Three papers used a quasi-experimental design. Nielsen et al. [32] applied rPMS over mid-thoracic roots in 12 persons with multiple sclerosis. They reported a global reduction of AS score for lower limb muscles, a significant decrease of soleus stretch reflex amplitude as measured by EMG (stretch velocity set at 90°/s) and an increase of its threshold velocity, thus supporting an overall decrease of spasticity. Also, MVC of plantar and dorsal flexors of ankle was significantly increased (29% and 27%, respectively) but this was not reproduced in the authors' randomized study [34]. The same group used the soleus H-reflex methods in participants suffering from multiple sclerosis and showed that rPMS applied directly at the thoracic vertebral midline (to depolarize spinal roots bilaterally) could reduce the spinal reflex hyperexcitability of spastic muscles [33]. The reduction of H-reflex amplitudes occurred a few minutes after rPMS application and lasted 28 min. The authors excluded a methodological bias because constant amplitude of M-responses was monitored thus preventing from variation of stimulus efficacy (Table 4). Krause et al. [19] tested 15 persons living with spasticity subsequent to a spinal disease. They applied rPMS over the lumbar spinal roots on the most affected side (most spastic lower limb) and reported that on both sides MAS score was immediately reduced and the first swing velocity increased (Wartenberg pendulum test). These changes reflecting spasticity decrease became significant at four and 24 hours after stimulation with a return to baseline in 11 participants re-tested 48 hours later.

Krause and Straube [21] conducted a case study in a 55-year-old spinal-cord injured person with spastic tone increase in both legs (12th thoracic vertebrae injured 4 years before enrollment). Stimulation was applied paravertebrally over the lumbar nerve roots once per week during 12 weeks. Real rPMS were administrated for nine sessions (three different frequencies tested, one per three sessions) and sham for three sessions (rPMS at very low intensity) using a randomized order (Table 3). The authors reported that the MAS scores were significantly reduced in both legs after each rPMS session (spasticity decrease with no relation to frequency used, no effect of sham) and the Wartenberg pendulum test presented an increase of swing decay rate (i.e. improvement of ''relaxation index'' [3]).

Over muscles

Struppler's group conducted two studies with a quasi-experimental design. Struppler et al. [44] applied rPMS over the paretic extensor indices proprius muscle in 52 persons who sustained a stroke two weeks to 10 years before enrollment. They showed a decrease of MAS scores (spasticity reduction) for hand muscles of more than 1.5 points in 36 persons and less than one point in 11. Scores remained unchanged in three persons and worsened (increased) in two. These differences between participants were not correlated with the location of lesion (cortical versus subcortical), the time since lesion or the age. Also, the amplitude and velocity of index finger movement during an extension task (electrogoniometric recordings) were increased and the EMG activity of the digit flexors and extensors was reduced. The authors suggested that rPMS reduced spasticity in the finger flexor muscles and rendered the index finger extension easier, thus requiring less activation of the index proprius. These after-effects persisted 24 hours after stimulation with a maximal peak after 2—4 hours. Struppler et al. [43] tested whether rPMS influenced the cerebral activation patterns in chronic stroke ($n = 8$ persons). RPMS were applied over the paretic extensor indices proprius muscle in two different sessions separated by a washout period. Previous findings [44] were replicated in the first session. In the second session, the authors used regional cerebral blood flow (rCBF) recorded by means of positron emission tomography (PET) scans of brain. Before rPMS, the finger extension task (as compared to rest) was abnormally associated with symmetrical bilateral increase of rCBF activity in the primary sensorimotor areas, premotor area (PM), supplementary motor area (SMA), neostriatum, cerebellum and in the contralateral parietal areas (PA). After rPMS on the paretic side, rCBF increase (as compared to rest) was higher in the (contralateral) lesioned hemisphere for PM, PA and motor cingulum. This was paralleled by an increase of movement amplitude and velocity during the index finger extension task.

The two last papers were case studies. Havel and Struppler [15] tested in a person with chronic stroke the ''closed-loop functional rPMS'' technique where stimulation was triggered at a specific level of EMG background (or joint position), for example during an index finger extension task. Results showed that rPMS applied over the innervation zone of the indices proprius muscle reduced the EMG activity of finger flexors and extensors and increased the amplitude and velocity of movement. Unfortunately, the details of experimental procedures were not mentioned and the authors refereed to previous papers written in German language. Bernhardt et al. [6] recruited one person with chronic stroke to test a mathematical algorithm used to quantify spasticity

changes on the basis of movement torque, range of motion and velocity. Results showed that rPMS slightly increased the dynamic components of index finger extension task with a decrease of the flexion components. The authors concluded that rPMS decreased spasticity of flexor muscles and eased the index finger extension.

Discussion

The aim of this work was to review the after-effects of rPMS on motor control in healthy individuals and in persons with motor impairment caused by central nervous system lesion or disease. The discussion that follows addresses the clinical relevance of rPMS in the field of clinical neurological research and the potential mechanisms of action.

Clinical relevance of rPMS

Change of spasticity after rPMS in people with CNS lesion or disease was a main outcome in all studies selected by the present review. Indeed, it is commonly acknowledged that spasticity limits the range of motion, thereby substantially contributing to the persistence of motor impairment [31]. However, this complex phenomenon is inconsistently defined and poorly measured [27]. Also, different components of spasticity (peripheral versus central) were tested in literature and no clear relation was proposed between the different outcomes measured, thus challenging the understanding of a clinical impact of rPMS. Nevertheless, spasticity decrease was consistently reported after rPMS over spinal roots (4 studies) and muscles (1 study) by means of the reduction of AS and MAS ordinal scores in persons with impaired motor control. One most interesting result was that spasticity reduction was accompanied by a decrease of activation of spastic and paretic muscle groups for a given movement amplitude and velocity. This supports that rPMS that decreases muscle resistance to stretch may contribute to improvement of movement dynamics. However, such effects did not outlast 24 hours [44].

But it is premature to conclude that rPMS applied over spinal roots or muscles had significant antispastic effects that may in turn improve the impaired motor control. The strength of evidences is limited due to the poor design of studies and the non-standardization of clinical tools used for evaluating spasticity, especially AS and MAS whose psychometric properties remain controversial [1,11]. More studies should be randomized and should combine EMG recordings of spastic muscles (Table 4). Statistical power and reliability of data remain weak and cannot lead to a consensus because literature on the topic is very scant to date, sample sizes are too small and protocols too different between studies.

Clinical relevance of rPMS is however supported by the elegant rCBF study conducted by Struppler et al. [43] (see Results). The authors showed that rPMS normalized the activation patterns of the fronto-parietal networks of motor planning and induced some functional improvement in stroke. Relation of fronto-parietal networks to functional recovery was already suggested in other treatment regimens [17,28–30,40] and therapies relying on movement-induced activation of proprioceptive afferents could further support the clinical relevance of rPMS. For example, constraint-induced therapy that forces the use of the paretic limb [37] or the task-specific training [2] that both produce massive sensory flows from paretic side mobilization have already demonstrated significant improvements of motor control even years after CNS lesion. Studies in healthy subjects and using functional magnetic resonance imaging (fMRI) have already shown that repetitive passive limb movements increased the activation of the contralateral structures involved in motor control, such as M1, SMA, cingulum, Brodmann area 40 and the ipsilateral cerebellum [8]. It was also reported in another rCBF study that repetitive wrist movements increased the activation of contralateral M1 and improved motor control, especially if movements were volitionally performed by the participants [26]. In persons with stroke, it was shown that a 4-week training of passive movements of the paretic arm (30 min daily) improved the performance of dexterity and grasping tasks and this was accompanied by an up-regulation of the activity of premotor, SMA, cerebellum, intraparietal sulcus and primary sensory cortices, as tested by fMRI [25].

Altogether, these studies suggest that training-induced recruitment of proprioceptive afferents up-regulates the excitability of the ipsilesional sensorimotor areas and thus has the potential to promote the function. This is in line with the hypothetical influence of rPMS on brain plasticity and function.

Possible mechanisms of action

Motor planning

Struppler et al. [41,43] proposed that rPMS induced proprioceptive inflows that influenced motor planning mechanisms at the cortical level. They also suggested that the activation of triceps brachii by rPMS [41] mimicked the cortical recruitment of forearm extensors usually involved in goal-directed movements, i.e. during tasks that required less elbow stabilization (decrease of antagonistic muscles tone). Conversely, the activation of biceps brachii by rPMS [41] may have mimicked the recruitment of forearm flexors usually engaged in functional tasks such as grasping and manipulating, i.e. tasks that require more elbow stabilization (increase of antagonistic muscles tone). The integration of proprioceptive information in motor drive may also contribute to synergistic control of muscles acting at a different joint in humans. For example, M1 representation of index finger abductors was inhibited during wrist extension (for hand aperture during forward-oriented movement) whereas released from inhibition (disinhibited) during wrist flexion (for precision grip) [12,13]. It was thus suggested that motor planning relay on proprioceptive inputs for the proximal-to-distal control of wrist joint and fingers [12,13]. Future work should question whether rPMS over a proximal muscle could influence motor planning of the more distal muscle to promote the control of interjoint muscle synergy.

Spinal versus cortical effects

Nielsen and Sinkjaer [33] did not observe any significant change of corticospinal excitability following the administration of rPMS ($n = 3$ healthy participants). Given that the H-reflex was systematically depressed after rPMS ($n = 9$ healthy participants), the authors first proposed that rPMS

induced pre-motoneuronal inhibition in the spinal networks rather than at the cortical level. They discussed further that the corticospinal facilitation observed in one subject (MEP increase) could have been masked in the others by the rPMS-induced inhibition surrounding the spinal motoneurons. Also, they notified that data interpretation in their very small sample size was limited because MEP and H-reflex may not have recruited the same circuits in spinal cord [33]. The inhibition of H-reflex following rPMS was not replicated in a recent randomized study [5]. However, between-study comparison seems irrelevant due to different sites of rPMS application (spinal roots [33] versus muscle [5]) and to different time-courses of measurement (H-depression maximal at 500 ms and up to 5 s post-rPMS [33] versus H-reflex tested at 2 min post-rPMS [5]). The most interesting information on the potential mechanisms of rPMS action at the cortical level came from Krause et al.'s TMS outcomes in healthy participants. They presented that rPMS applied over the cervical roots lengthened cSP [20,22] and increased the MEP amplitudes and the short-interval intracortical inhibition (SICI) [22]. These changes likely reflected dynamic plastic phenomena of pure cortical origin, given that cSP and SICI relay on the activity of M1 inhibitory interneurons working with $GABA_B$ and $GABA_A$ receptors, respectively [10,13,23,36]. These findings suggest that rPMS could have influenced mechanisms of different nature in the hemisphere contralateral to the side stimulated, such as $GABA_A$/$GABA_B$ inhibition and glutamatergic facilitation, all known to balance M1 homeostasis [10,36]. Such changes akin long-term potentiation (LTP) and depression (LTD) at the cortical synapses are integral to learning processes in brain and may contribute to understand how rPMS can improve the function in people with central neurological disorders, including the decrease of spasticity via an influence on spinal networks. Future studies ought to better address these mechanisms underlying rPMS action on spinal and cortical networks in order to better understand the effects on motor control.

Hemispheric homeostasis and balancing

The massive proprioceptive signals triggered by rPMS may have increased sensory inflow from subcortical levels and generated movement-like activity in the contralateral somesthetic and motor cortical areas. This hypothesis is supported by the TMS data of Krause et al.'s studies in healthy participants [20,22] and by the rCBF data of Struppler et al. in stroke [43]. In line, it is possible to say that M1 excitability was influenced by thalamocortical and corticocortical networks. This activity-dependent modification of cortical synapses to undergo LTP (increase of activation) or LTD (decrease) is refereed to as metaplasticity that maintains homeostasis of cortical excitability in healthy humans [14]. Any interference, such as rPMS after-effects, may thus trigger metaplasticity to balance brain homeostasis, thus modulating M1 cell excitability (including GABAergic and glutamatergic neurons) and influencing M1 function and motor control. Of consideration is the counter-intuitive discrepancy between the after-effects specific to side stimulated (only in the contralateral hemisphere) and the bilateral improvements when only one side was stimulated. The lack of change in M1 ipsilateral to the side stimulated [22] may witness that transcallosal or subcallosal routes were not involved after rPMS. Does this suggest that motor improvement observed on the non-stimulated side (in cases of bilateral improvements) are only explained by the influence of rPMS on the ipsilateral networks of spinal cord? In fact, the few TMS experiments that reported changes in the contralateral hemisphere only were conducted in healthy people [20,22]. Hemispheric activity is *a priori* balanced in normal conditions and interhemispheric connections may rapidly compensate any rPMS interference (return to baseline), thus challenging the detection of effects in the hemisphere ipsilateral to the side of rPMS administration. The picture could be different in brain-injured persons with imbalanced activity between ipsi- and contralesional hemispheres and with maladaptive reorganization of the lesioned brain [35]. Therefore, future clinical studies should explore the influence of rPMS on hemispheric balancing and test whether such mechanism favors motor improvement in physiopathology.

Conclusions

This review screened the work and practice currently published on the use of rPMS in persons with motor impairments and on the potential mechanisms of action underlying the effects. Despite the lack of clear conclusions, all studies reported spasticity reduction leading or not to improvement of biomechanical components of motor control. It was also strongly suggested that peripheral afferents recruited by rPMS had the potential to influence cerebral activation patterns and motor control. The review thus encourages future randomized sham-controlled and double-blinded designed studies to further test rPMS influence on the impaired motor control. The future research should combine neurophysiological and clinical tools to test acute, delayed and long lasting changes, at the cortical and spinal levels, rPMS over the roots, nerves and muscles, and finally evaluate whether target outcomes are sensitive enough to detect and follow-up functional improvement in people living with muscle spasticity and paresis. This will foster our knowledge on CNS plasticity and state whether rPMS is of relevant interest in neurorehabilitation.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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